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Concurrent with the recent developments in neural network theories of learning and memory has been the experimental demonstration of experience-dependent synaptic plasticity at the highest level of the mammalian nervous system, the cerebral cortex. A neurobiological problem of extraordinary interest is to identify the molecular mechanisms which underlie this process of cortical modification. For the complex forms of plasticity evoked in neocortex by changes in the sensory environment, an essential first step in sorting out the various possibilities is to derive a set of rules that can adequately account for the observed modifications. These rules serve as a guide towards identifying candidate mechanisms that can then be tested experimentally. Hence, it can be seen that two lines of inquiry

one concerning neural network theory, the other concerning molecular mechanisms of synapse modification--converge at the level of the modification rule.

We have proposed such a modification rule to explain the rich body of experimental evidence available on the experience-dependent plasticity of the feline visual cortex during early postnatal development. This theoretical form of modification is able to account for the results of a wide variety of deprivation experiments, and has led to a number of predictions that appear to have been confirmed by more recent experiments. In this chapter we shall illustrate how this theory has interacted with experiment to suggest a possible molecular basis for synapse modification in the visual cortex.

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MOLECULAR MECHANISMS FOR SYNAPTIC MODIFICATION IN THE VISUAL CORTEX: INTERACTION BETWEEN THEORY AND EXPERIMENT[1]

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Introduction.

As this volume attests, we have witnessed in the last several years an explosion of interest in computational "neural network" models of learning and memory. A common feature of these models is that information is stored in the "synaptic" coupling between vast arrays of converging inputs ("neurons"). Such distributed memories can be shown to display many properties of human memory: recognition, association, generalization, and resistance to the partial destruction of elements within the network. An interesting feature of these models is that their performance is constrained by the patterns of connectivity within the network. This reinforces the view, long held by neurobiologists, that an understanding of neural circuitry holds a key to elucidating brain function. Hence, modern neural network models attempt to incorporate the salient architectural features of the brain regions of interest. However, another crucial aspect of network function concerns the way that the synaptic junctions are modified to change their strength of coupling. Most models have assumed a form of modification based on Hebb's (1949) proposal that synaptic coupling increases when the activity of converging elements is coincident. Variations upon this venerable "learning rule" have been enormously successful in simulations of various forms of animal learning. However, this work has also shown that just as network behavior depends on connectivity, the capabilities of the network vary profoundly with different modification rules. What forms of synaptic

modification are most appropriate? Again, we must look to the brain for the answer.

Concurrent with the recent developments in neural network theories of learning and memory has been the experimental demonstration of experience-dependent synaptic plasticity at the highest level of the mammalian nervous system, the cerebral cortex. A neurobiological problem of extraordinary interest is to identify the molecular mechanisms which underlie this process of cortical modification. For the complex forms of plasticity evoked in neocortex by changes in the sensory environment, an essential first step in sorting out the various possibilities is to derive a set of rules that can adequately account for the observed modifications. These rules serve as a guide towards identifying candidate mechanisms that can then be tested experimentally. Hence, it can be seen that two lines of inquiry -- one concerning neural network theory, the other concerning molecular mechanisms of synapse modification -- converge at the level of the modification rule.

We have proposed such a modification rule to explain the rich body of experimental evidence available on the experience-dependent plasticity of the feline visual cortex during early postnatal development. This theoretical form of modification is able to account for the results of a wide variety of deprivation experiments, and has led to a number of predictions that appear to have been confirmed by more recent experiments. In this chapter we shall illustrate how this theory has

interacted with experiment to suggest a possible molecular basis for synapse modification in the visual cortex.

Analysis of Visual Cortical Plasticity

Neurons in the striate cortex, area 17, of normal adult cats are sharply tuned for the orientation of an elongated slit of light and most are activated by stimulation of either eye (Hubel and Wiesel, 1962). Both of these properties -- orientation selectivity and binocularity -- can be modified by visual experience during a critical period of early postnatal development which, in the cat, extends from approximately 3 weeks to 3 months of age (Sherman and Spear, 1982; Frégnac and Imbert, 1984). The problem of visual cortical plasticity can be divided into three parts. *First*, what controls the onset and duration of the critical period? The answer to this question is unknown at present, but some interesting possibilities include specific patterns of gene expression (Neve and Bear, 1988; Sur et al., 1988) which may be under hormonal control (Daw, et al., 1988). *Second*, within the plastic period, what factors enable synaptic modification to proceed? This question is prompted by the observation that experience-dependent modifications of visual cortex seem to require that animals attend to visual stimuli and use vision to guide behavior (Singer, 1979). The best candidates for "enabling factors" are the neuromodulators acetylcholine and norepinephrine that are released in visual cortex by fibers arising from neurons in the basal forebrain and brain stem (Bear and Singer, 1986). *Third*, when modifications are allowed to occur during the critical period, what

controls their direction and magnitude? This is where the interaction between theory and experiment has been most fruitful, and this is the question we shall address in this chapter.

The visual cortex is a well differentiated structure with six layers and an intricate intracortical connectivity whose details remain only poorly understood (Martin, 1987). Nonetheless, it is known that the large majority of neurons in layers III, IV and VI receive direct monosynaptic input from the lateral geniculate nucleus (Toyama et al., 1974; Ferster and Lindstrom, 1983; Martin, 1987). The receptive fields of lateral geniculate nucleus (LGN) neurons resemble those of retinal ganglion cells: they are monocular and, for the most part, non-oriented. Hence, cortical binocularity results from the convergence of LGN inputs onto cortical neurons. This convergence is not equal for every neuron and the term "ocular dominance" (OD) is used to describe the relative contribution of the two eyes to the cell's response. Although intracortical inhibition is acknowledged to play an important role in the refinement of orientation selectivity (Sillito et al., 1980; Ramoa et al., 1988), there is evidence that this property is also generated by the pattern of convergence of LGN inputs onto cortical neurons (Hubel and Wiesel, 1962; Ferster, 1986). Thus, in the first stage of the theoretical analysis, there is some justification for stripping away much of the complexity of the striate cortex, and considering a single cortical neuron receiving converging inputs from the two eyes via the LGN (figure 1).

Cortical binocularity can be disrupted by a number of manipulations of visual experience during the critical period. For example, if the eyes are misaligned by severing one of the extraocular muscles, then cortical neurons lose their binocularity and become responsive only to one eye or the other (Blakemore and van Sluyters, 1974). Likewise, if one eye is deprived of patterned visual input (usually by suturing the eyelid closed), the ocular dominance of cortical neurons shifts such that most cells become responsive exclusively to stimulation of the open eye Wiesel and Hubel, 1965). These changes in cortical binocularity can occur quite rapidly and are presumed to reflect the modification of the synaptic effectiveness of the converging inputs from the two eyes.

The consequences of binocular deprivation (BD) on visual cortex stand in striking contrast to those observed after monocular lid closure. Firstly, BD lead to a loss of orientation selectivity, an effect never seen after monocular deprivation (MD). Secondly, while a week of MD during the second postnatal month leaves few neurons in striate cortex responsive to stimulation of the deprived eye, most cells remain responsive to visual stimulation through either eye after a comparable period of BD (Wiesel and Hubel, 1965). Thus, it is not merely the absence of patterned activity in the deprived geniculocortical projection that causes the decrease in synaptic efficacy after MD.

Gunther Stent, in an influential 1973 paper, pointed out that one difference between MD and BD is that only in the former instance are cortical neurons active (figure 1). This consideration led him to

hypothesize that evoked postsynaptic activity is a necessary condition for synaptic modification in the striate cortex, and the sign of the change (+ or -) depends on the concurrent level of presynaptic input activity. Synaptic disconnection of afferents deprived of patterned activity occurs only after MD because only under these conditions are cortical neurons still driven by visual stimulation (through the open eye). Subsequent work suggested, however, that the generation of action potentials in a cortical neuron does not ensure that ocular dominance modifications will occur after MD (Kasamatsu and Pettigrew, 1979; Singer, 1982; Bear and Singer, 1986). To reconcile these data with the Stent model, Wolf Singer (1979) introduced the idea that there is a critical level of postsynaptic activition that must be reached before experience-dependent modifications will occur, and that this threshold is higher than the depolarization required for somatic sodium-spikes. A similar type of modification rule has been proposed for the activity-dependent synaptic changes in the dentate gyrus (Levy and Golbert, this volume). According to this hypothesis, the "enabling factors" mentioned above could be any inputs that render cortical neurons more excitable and hence more likely to exceed this "plasticity threshold" (figure 2; Bear and Singer, 1986; Greuel et al., 1987).

This hypothesis is challenged by the finding that the effects of MD can be rapidly reversed by opening the deprived eye and suturing closed the other eye. Such a "reverse suture" leads to a robust OD shift back to the newly opened eye, even though visually evoked postsynaptic activity

is low or absent at the time of the reversal (because the only source of patterned visual input to cortical neurons is the functionally disconnected afferents from the unsutured eye). The effects of cortical disinhibition on OD modification are also difficult to explain by this hypothesis. Intracortical infusion of the $GABA_A$ receptor antagonist bicuculline, which decreases orientation selectivity and generally increases cortical responsiveness, retards rather than facilitates the functional disconnection of the deprived eye after MD (Ramoa et al., 1988).

Reiter and Stryker (1988) recently performed a direct test of the hypothesis that postsynaptic activation is simply "permissive" to the process of synaptic modification. They continuously infused muscimol into striate cortex as kittens were monocularly deprived for 7 days. Muscimol, a $GABA_A$ receptor agonist, prohibits cortical neurons from firing presumably by clamping the membrane near the chloride equilibrium potential. With the muscimol still present in cortex, they mapped the cortex to determine the extent of activity blockade. They found that all cortical cell responses were eliminated within several mm of the infusion cannula, even though LGN fiber activity was readily demonstrated. When the muscimol wore off, they performed an ocular dominance assay in the zone of cortex whose activity had been blocked. They observed an unexpected ocular dominance shift toward the *deprived* eye; that is, most neurons were no longer responsive to stimulation of the retina that had been more active during the period of MD (figure 3).

Although all experiments involving chronic intracortical drug infusion must be interpreted with extreme caution, these muscimol results seem to indicate that OD modifications can occur in the absence of evoked action potentials. Further, the data suggest that patterned presynaptic activity can lead to either an increase or a decrease in synaptic strength, depending on whether or not the target neurons are allowed to respond.

An alternative theoretical solution to the problem of visual cortical plasticity, first propsed by Cooper, Liberman and Oja (CLO) in 1979, is able to account for these varied results. According to this theory, the synaptic efficacy of active inputs increases when the postsynaptic target is concurrently depolarized beyond a "modification threshold", θ_M. However, when the level of postsynaptic activity falls below θ_M, then the strength of active synapses decreases.

An important additional feature was added to this theory in 1982 by Bienenstock, Cooper and Munro (BCM). They proposed that the value of the modification threshold is not fixed, but instead varies as a non-linear function of the average output of the postsynaptic neuron. This feature provides the stability properties of the model, and is necessary to explain for example why the low level of postsynaptic activity caused by binocular deprivation does not drive the strengths of all cortical synapses to zero.

This form of synaptic modification can be written:

$$dm_j / dt = \phi (c, \bar{c}) d_j \qquad [1]$$

where m_j is the efficacy of the j[th] LGN synapse onto a cortical neuron, d_j is the level of presynaptic activity of the j[th] LGN afferent, c is the level of activation of the postsynaptic neuron[1], and $\bar{c}$ is the time average of postsynaptic neuronal activity (d_j and c are viewed as averages over about half a second; $\bar{c}$ is the average over a period that could be several hours). The crucial function, ϕ, is shown in figure 4.

One significant feature of this model is the change of sign of ϕ at the modification threshhold, θ_M. When the j[th] synapse is active ($d_j > 0$) and the level of postsynaptic activation exceeds the modification threshold ($c > \theta_M$), then the sign of the modification is positive and the strength of the synapse increases. However, when the j[th] synapse is active and the level of postsynaptic activation slips below the modification threshold ($c < \theta_M$), then the sign of the modification is negative and the strength of the synapse decreases. Thus, "effective" synapses are strengthened and "ineffective" synapses are weakened, where synaptic effectiveness is determined by whether or not the presynaptic pattern of activity is accompanied by the simultaneous depolarization of the target dendrite beyond the modification threshold.

According to this model, synaptic weakening requires that the postsynaptic membrane potential falls below the modification threshold. Thus, during monocular deprivation, the deprived-eye synapses will

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[1] In a linear approximation, $c = \mathbf{m}^l \cdot \mathbf{d}^l + \mathbf{m}^r \cdot \mathbf{d}^r$, where $\mathbf{d}$ and $\mathbf{m}$ are vectors representing the total input activity and synaptic weight of the array of fibers carrying information from the left or right eyes.

decrease in strength each time the open-eye input activity does not strongly depolarize the cortical neuron. This occurs when the input patterns conveyed by the open-eye afferents fail to match the stimulus selectivity of the neuron. Therefore, the theory predicts a relationship between the ocular dominance shift after MD and the degree of orientation tuning of cortical neurons.

The application of bicuculline to cortex, by reducing the stimulus selectivity of cortical neurons, increases the probability that the unstructured activity from the deprived eye correlates with cortical activation at or beyond the modification threshold. Therefore, in agreement with experimental results (Ramoa, et al., 1988), the theory predicts that no synaptic disconnection of deprived eye afferents would occur when cortex is disinhibited. On the other hand, muscimol treatment would suppress the postsynaptic response well below the modification threshold regardless of the afferent input. The theory predicts that under these conditions there will be synaptic weakening at a rate proportional to the level of input activity which, in accordance with experimental observations (Reiter and Stryker, 1988), would yield an ocular dominance bias toward the less active eye.

Another significant feature of this theory is that the value of the modification threshold (θ_M) is not fixed, but instead varies as a non-linear function of the average output of the cell ($\bar{c}$). In a simple situation:

$$\theta_M = (\bar{c})^2 \qquad [2]$$

This feature allows neuronal responses to evolve to selective and stable "fixed points" (Bienenstock et al., 1982). However, more importantly in the context of the present discussion, it is this feature of the theory that accounts for the differences between MD and BD. Deprivation of patterned input leads to synaptic disconnection after MD because open eye input activity continues to drive cortical neurons sufficiently to maintain θ_M at a high value. However, because average cortical activity falls during BD, the value of θ_M approaches zero (figure 5). In this case, the unstructured input activity causes synaptic strengths to perform a "random walk" (Bienenstock et al., 1982). Consequently, the theory also predicts the loss of orientation selectivity that has been observed after BD.

The sliding modification threshold also permits a theoretical explanation for the effects of reverse suture. The output of a cortical neuron in area 17 approaches zero just after the reversal since its only source of patterned input is through the eye whose synapses had been weakened as a consequence of the prior MD. However as $\bar{c}$ diminishes, so does the value of θ_M. Eventually, the modification threshold attains a value *below* the small output that is evoked by stimulation of the unsutured eye, allowing these active synapses to increase in strength. If θ_M does not adjust to the new average firing rate too rapidly, the cell's response to the previously open eye will diminish *before* its response to the newly opened eye increases.

Analysis and computer simulations using this theoretical form of synaptic modification are able to reproduce the classical results of manipulating visual experience during the critical period (Bienenstock et al., 1982; Clouthier, Bear and Cooper, unpublished). The theory can account for the acquisition of orientation selectivity with normal visual experience as well as the effects of monocular deprivation, binocular deprivation and reverse suture. In addition, as we have seen, this form of modification offers a solution to the seemingly paradoxical effects of pharmacologically manipulating cortical activity during monocular deprivation. It is worthwhile to note that there need not be any modification of inhibitory circuitry to account for the experience-dependent modifications in striate cortex using this theory (Cooper and Scofield, 1988). This is reassuring since experimental efforts to uncover modifications of inhibitory circuits in visual cortex have consistently yielded negative results (Singer, 1977; Bear et al., 1985; Mower et al., 1987).

The success of this theory encourages us to ask whether this form of synaptic modification has a neurobiological basis. The remainder of this chapter summarizes the progress we have made in answering this question (as of October, 1988).

A molecular mechanism for increasing synaptic strength in visual cortex.

According to the theory, synaptic strength increases when presynaptic inputs are active ($d > 0$) *and* the target dendrite is

depolarized beyond the modification threshold ($c > \theta_M$). The relevant measure of input activity is likely to be the rate of transmitter release at the geniculo-cortical (and excitatory intracortical) synapses. While the exact identity of this transmitter substance is still not known with certainty, available evidence indicates strongly that it acts via excitatory amino acid (EAA) receptors (Tsumoto et al., 1986). This leads to the following question: When EAA receptors are activated, what distinquishes the response at depolarized membrane potentials ($c > \theta_M$) from the response at the resting potential ($c < \theta_M$)?

As elsewhere, cortical EAA receptors fall into two broad categories: NMDA and non-NMDA. Both types of EAA receptor are thought to coexist subsynaptically (figure 6). The ionic conductances activated by non-NMDA receptors at any instant depend only on the input activity, and are independent of the postsynaptic membrane potential. However, the ionic channels linked to NMDA receptors are blocked with Mg^{++} at the resting potential, and become effective only upon membrane depolarization (Nowak et al., 1984; Mayer and Westbrook, 1987). Another distinctive feature of the NMDA receptor channel is that it will conduct calcium ions (Dingledine, 1984; MacDermott, et al., 1986). Hence, the passage of Ca^{++} through the NMDA channel could specifically signal when pre- and postsynaptic elements are concurrently active. These considerations have led us to propose that θ_M relates to the dendritic membrane depolarization at which presynaptic activity leads to a critical postsynaptic Ca^{++} flux, and that the Ca^{++}, acting as a second

messenger, leads to an enhancement of synaptic strength (Bear, et al., 1987).

Data from *in vitro* slice experiments lend strong support to this hypothesis. Long-term potentiation (LTP) of synaptic effectiveness which normally results from tetanic afferent stimulation, cannot be induced in either the CA1 subfield of the hippocampus (Collingridge et al., 1983; Harris et al., 1984) or the visual cortex of rats (Artola and Singer, 1987; Kimura et al., 1988) and kittens (Connors and Bear, 1988) when NMDA receptors are blocked (see also Granger and Lynch, this volume). On the other hand, the application of N-methyl-D-aspartate (the selective agonist that gives the "NMDA" receptor its name) to hippocampal slices can induce a form of synaptic potentiation that can last for 30 minutes (Kauer et al., 1988) or longer (Thibault et al., 1988). The idea that elevations in postsynaptic [Ca^{++}] trigger the increase in synaptic strength is supported by the finding that intracellular injection of the Ca^{++} chelator EGTA blocks the induction LTP in CA1 pyramidal cells (Lynch et al., 1983). Further, the intracellular release of Ca^{++} from the photolabile calcium chelator nitr-5 produces a long-lasting potentiation of synaptic transmission that resembles LTP (Malenka et al., 1988). Taken together, these data indicate that the calcium conductance mediated by the NMDA receptor plays a special role in strengthening synaptic relationships in the cortex.

The possible involvement of NMDA receptors in the experience-dependent modification of visual cortex was examined in a recent series of experiments carried out in Wolf Singer's laboratory (Kleinschmidt et

al., 1987; Bear et al., 1987). The selective NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (APV) was infused continuously into striate cortex as kittens were monocularly deprived. After 7 days the APV treatment was stopped and the cortex 3-6 mm away from the infusion cannula was assayed electrophysiologically for changes in ocular dominance and orientation selectivity. The chronic APV treatment was found to produce a concentration dependent increase in the percentage of neurons with binocular, unoriented receptive fields (figure 7). Qualitatively, the results resembled those expected in visual cortex after *binocular deprivation*. Yet, electrophysiological recordings during the week of APV infusion revealed that NMDA receptor blockade did not eliminate visual responsivenenss in striate cortex.

According to the "NMDA hypothesis" (Bear et al., 1987) APV infusion should, in effect, raise the value of θ_M. If cortical neurons remain moderately responsive to visual stimulation, but are unable to achieve θ_M, then a theoretical consequence will be a modified "random walk"[1]. This will result in a loss of orientation selectivity and a slow loss of synaptic efficacy -- a result similar to that of BD.

However, if the postsynaptic response is low, the predicted effect of NMDA receptor blockade during MD is a loss of synaptic strength at a rate proportional to the level of presynaptic activity. This could explain

[1] This effect requires that $\mathbf{d}$ have positive and negative components. According to BCM, when input fibers are spontaneously active, $\mathbf{d} = 0$; when they carry noise (an effect of lid suture or dark rearing), $\mathbf{d}$ averages to zero. In a patterned input environment, $\mathbf{d}$ has positive and negative components, but the average is likely to be greater than zero.

the observations of Reiter and Stryker (1988), assuming that the hyperpolarization produced by muscimol treatment renders cortical NMDA receptors ineffective. In a more recent study, APV infusion was also found to have this effect (Bear et al., 1987). In this experiment, the cortex was studied at various distances from the infusion cannula after two days of MD and APV treatment (figure 8). The OD of units studied within 3 mm of the cannula, where APV concentrations are highest, was found to be strongly biased toward the deprived eye. Most neurons were binocular at sites ≥ 4 mm from the cannula. And, as expected, the OD of cells recorded in the contralateral control cortex was shifted to the open eye.

A molecular mechanism for decreasing synaptic strength in visual cortex.

The theory states that when the postsynaptic depolarization falls below the modification threshold then synaptic strengths decrease at a rate proportional to input activity. What signals input activity when the membrane is hyperpolarized and the NMDA channel is fully blocked with Mg^{++}?

Certainly the activity of non-NMDA receptors reflects the amount of transmitter release regardless of whether or not NMDA receptors are effective. This has inspired us to search for an intracellular second messenger other than Ca^{++} that depends solely on the activation of non-NMDA receptors. One possibility has been suggested by recent investigations of EAA mediated phosphoinositide (PIns) turnover in the

cerebral cortex (figure 9). This work has shown that during a finite period of postnatal development, stimulation of rat hippocampus (Nicoletti et al., 1986) or neocortex (Dudek et al., 1988) with glutamate or ibotenate (but not NMDA) leads to the hydrolysis of phosphatidyl inositol-4,5 biphosphate to produce inositol triphosphate (IP_3) and diacyl glycerol (DG). Both IP_3 and DG function as intracellular second messengers (Berridge, 1984).

Of particular interest is the age-dependence of the EAA stimulated PIns turnover. Dudek and Bear have found very recently that in the kitten striate cortex, there is a striking correlation between the developmental changes in ibotenate-stimulated PIns hydrolysis and the susceptibility of visual cortex to monocular deprivation (figure 10). It is difficult to resist the conclusion that this mechanism plays a central role in the modification of cortical synapses during the critical period.

At present there is not a shred of evidence to indicate what this role might be. However, the theory suggests one interesting possibility. Namely, that the stimulation of PIns hydrolysis by non-NMDA receptor activation leads to a decrease in synaptic strength. Accordingly, changes in synaptic efficacy would result from changes in a balance between NMDA receptor mediated Ca^{++} entry and non-NMDA receptor mediated PIns turnover (Bear, 1988). Synaptic strength would increase when the NMDA signal exceeds the non-NMDA signal. This occurs when the input activity is coincident with strong depolarization ($c > \theta_M$). Synaptic strength would decrease when input activity consistently correlates with

insufficient membrane depolarization ($c < \theta_M$) because the non-NMDA signal exceeds the NMDA signal.

Although this hypothesis was formulated purely on theoretical grounds (Bear, 1988), some recent work in Carl Cotman's laboratory supports the idea that the second messenger systems linked to NMDA and non-NMDA receptors might be antagonistic (Palmer et al., 1988). They find in the neonatal hippocampus that NMDA inhibtis EAA-stimulated PIns turnover in a Ca^{++} dependent fashion.

A molecular mechanism for the sliding modification threshold.

A critical feature of this theory of synapse modification is that θ_M, the level of dendritic depolarization at which the sign of the synaptic modification changes, floats as a non-linear function of average cell activity ($\bar{c}$). θ_M is "quasi-local", in the sense that it has the same value at all synapses on a given neuron (Bienenstock et al., 1982; Bear et al., 1987). Thus, we search for a molecular mechanism which would provide a signal that is (1) uniformly available throughout the dendritic tree and (2) is regulated by average neuronal activity. One mechanism that fits this description is the activity-dependent expression of specific neuronal genes (Black et al., 1988).

Neve and Bear (1988) have recently demonstrated that visual experience can indeed regulate gene expression in the kitten striate cortex. For example, the mRNA transcript for the neuronal growth associated protein GAP43 (Benowitz and Routtenberg, 1987) was found to be increased by rearing kittens in complete darkness. Moreover, this

increase in GAP43 gene expression was reversed by only 12 hours of light exposure (figure 11).

According to the molecular model developed so far, adjustments of the modification threshold conceivably could occur by changing the balance between the synaptic reward and punishment signals generated by the NMDA and non-NMDA receptors, respectively. Therefore, we have focused our search on the products of activity-dependent gene expression that could potentially affect this balance. Calcium-calmodulin dependent protein kinase II (CaM kinase II) is one such molecule. CaM kinase II is a major constituent of the postsynaptic density, and is a critical link in the biochemical cascade of events that is triggered by Ca^{++} entry. It is not diffcult to imagine how changes in the level of CaM kinase might alter the effectiveness of NMDA receptor mediated Ca^{++} signals. Indeed, in the striate cortex of dark reared kittens Neve and Bear (1988) find that the CaM kinase transcript is elevated over control levels. Similarly, Hendry and Kennedy (1988) found in primate visual cortex that immunoreactive CaM kinase II is increased in columns deprived of normal input after monocular deprivation.

Another way to change the balance between NMDA and non-NMDA receptors is to alter the effectiveness of the receptors in generating second messengers. For the NMDA receptor this could be accomplished in several ways including changing the number or affinity of the receptors, the number or affinity of the allosteric binding sites for glycine and zinc (Lodge et al., 1988), and the phosphorylation state of the

channel protein (MacDonald, et al., 1988). Due to this abundance of potential regulatory mechanisms, we decided to address this issue using a functional assay of receptor effectiveness: NMDA-stimulated uptake of ^{45}Ca into slices of kitten visual cortex maintained *in vitro* (Sherin et al., 1988).

We predicted that under conditions where the modification threshold had a low value, slices of visual cortex should show heightened sensitivity to applied NMDA. One such condition is binocular deprivation. In figure 12, the NMDA stimulated calcium uptake of slices from normal kittens is compared with that measured in slices from animals binocularly deprived for 4 days. There is a significant *decrease* in the maximum Ca^{++} uptake evoked by saturating concentrations of NMDA in slices from BD kittens (figure 12A). One simple explanation for this result is a decrease in the total number of NMDA receptors in BD striate cortex, perhaps reflecting a global loss of synaptic strength. However, if this is the case, then uptake in slices from BD animals should be lower at all concentrations of NMDA. Yet, at low concentrations (12.5-25 μM) the measured uptake is the same for normal and BD cortex. According to this line of reasoning, this difference in calcium uptake kinetics indicates that the remaining NMDA receptors might be relatively more effective in BD cortex. This is illustrated in figure 12B, where uptake from control and BD kittens is expressed as a percentage of maximal uptake. It is clearly premature to draw any firm conclusions from these data because calcium uptake depends on a complex interaction between NMDA and voltage-

gated calcium entry, as well as on calcium extrusion and sequestration. Nonetheless, this work indicates that this question is worth exploring in more detail, perhaps now with receptor binding techniques.

Although still in its infancy, this work has already been able to show that the changes in average cortical activity produced by visual deprivation lead to alterations in gene expression and NMDA stimulated calcium uptake. Thus, the biological precedent for a sliding threshold mechanism in striate cortex is now established. Future work will be aimed at teasing out which changes are relevant for experience-dependent synaptic modification.

A molecular model that captures the essence of the BCM theory is presented in figure 13. According to this model, the efficacy of an active synapse increases when the postsynaptic signal generated by NMDA receptor activation ("N", probably Ca^{++}) exceeds the signal produced by the activation of non-NMDA receptors ("Q", possibly a product of PIns turnover). This occurs when the summed postsynaptic depolarization ($\Sigma m_j d_j$) is greater than the modification threshold (θ_M). When the level of postsynaptic depolarization falls below the modification threshold, $N < Q$ and the synapse weakens. Considered in this way, the modification threshold becomes the critical level of postsynaptic depolarization at which the NMDA receptor dependent Ca^{++} flux is sufficient to balance the synaptic "punishment" produced by activation of non-NMDA receptors. We imagine that whether or not a given Ca^{++} flux is "sufficient" possibly depends on the availability of postsynaptic Ca^{++}-activated

enzymes which, in turn, depends on the regulation of gene expression by average neuronal activity (Bear, 1988).

Generalization to a many-neuron system

The BCM theory of synaptic modification deals with a single cortical neuron receiving input from the lateral geniculate nucleus only. The second stage of the theoretical analysis requires that relevant intracortical connections be incorporated into the model. Consider the simple network illustrated in figure 14 (A) in which cortical neurons (both excitatory and inhibitory) receive input from the LGN and from each other. The integrated output of the i^{th} neuron (in the linear region) may be written

$$c_i = \mathbf{m}_i^l \cdot \mathbf{d}^l + \mathbf{m}_i^r \cdot \mathbf{d}^r + \sum L_{ij}\, c_j \qquad (3)$$

where the term $\sum L_{ij}\, c_j$ is the sum of the output from other cells in the network multiplied by the strength of their synapses on the i^{th} cell. It is assumed that the intracortical synapses do not modify, or modify only slowly, and that the net influence of the intracortical connections is inhibitory.

Analysis of geniculo-cortical modification in this network leads to a very complex set of coupled nonlinear stochastic equations (Scofield and Cooper, 1985). However a mean-field approximation permits dramatic simplification of these equations (Cooper and Scofield, 1988). In a manner similar to the theory of magnetism, the individual effects of other cortical neruons are replaced by their average effect. The integrated output of the i^{th} cortical neuron now becomes

$$c_i = (\mathbf{m}_i^l - \alpha^l)\cdot \mathbf{d}^l + (\mathbf{m}_i^r - \alpha^r)\cdot \mathbf{d}^r \quad (4a)$$

$$= (m_i - \alpha)d \quad (4b)$$

where $-\alpha$ represents the average inhibitory influence of the intracortical connections (figure 14 B).

There is an interesting theoretical consequence of assuming that each cortical neuron is under the influence of an inhibitory mean field. According to the BCM theory, monocular deprivation leads to convergence of geniculocortical synapses to a state where stimulation of the deprived eye input results in an output that equals zero ($c = 0$). However, with average network inhibition, the evolution of the cell to this state does not require that the efficacy of deprived-eye synapses be driven completely to zero. Instead, these excitatory synapses will evolve to a state where their influence is exactly offset by intracortical inhibition. Thus, the removal of intracortical inhibition in this network would reveal responses from otherwise ineffective inputs. This result is in accordance with the experimental observation of "unmasking" of synapses when the inhibitory effects of GABA are antagonized with bicuculline (Duffy et al., 1976).

No revisions in the molecular model (figure 13) are required to incorporate the mean field theory, although it is clear that the balance between NMDA and non-NMDA receptor activation will vary depending on network inhibition. α depends on the average connection strengths of intracortical synpases (L_0), which are assumed to not be modified, and the spatial average of the LGN-cortical synapses "viewing" the same

point in visual space, which changes only slowly (in comparison with the modification of m_j). Hence, in simulations of the evolution of the cortical network, α remains relatively constant from iteration to iteration.

However, it is interesting to note that if the value of α were to vary as a function of the timing of coherent inputs, the model could account for the changes in hippocampal synapses induced by patterned electrical stimulation (see Granger and Lynch, this volume). Input activity coincident with $\alpha = 0$ (which, according to Larson and Lynch (1986), occurs when hippocampal inputs are stimulated at theta frequency) would be more likely to depolarize the neuron beyond θ_M and consequently would increase synaptic strength (figure 15 A). Conversely, input activity patterned in such a way as to coincide with strong inhibition ($\alpha >> 0$), should yield a depression of synaptic strength (figure 15 B).

Concluding remarks

We have presented a theoretical model for synaptic modification which can explain the results of normal rearing and various deprivation experiments in visual cortex. Further, we have shown that crucial concepts of the theory have a plausible molecular basis. Although some of this work is in a preliminary state, it provides an excellent illustration of the benefit of the interaction of theory with experiment.

Theory enables us to follow a long chain of arguments and to connect in a fairly precise way, various hypotheses with their consequences. It forces us to refine our language so that questions can

be formulated with clarity and precision. Experiment focuses our attention on what is real; it separates what might be from what is; it tells us what must be explained, and what is possible among explanations.

The theoretician who develops his arguments with close attention to the experimental results may thereby create a concrete structure of sufficient clarity so that new questions, of great interest and amenable to experimental verification, become apparent. The sliding threshold provides an excellent example. The concept of the modification threshold was introduced by CLO and BCM to account for such classical results as the development of neuron selectivity in normal visual environments and the various deprivation experiments. This led to unexpected theoretical consequences such as the correlation between ocular dominance and selectivity (now experimentally verified) and is sufficient to explain the results of the various pharmacological experiments.

Once convinced of the utility of this concept, the question of its physical basis became of great interest. This led us to the efforts concerning NMDA receptors, PIns turnover and regulation of gene expression in visual cortex [on a grander scale, Gregor Mendel's concept of the gene, introduced to explain the color of the sweet peas in his garden, was sufficiently attractive to provoke the activity that finally resulted in our present understanding of gene structure]. And, as is almost always the case for an idea of richness, when the physical basis of the abstract concept is finally delineated, it contains a wealth of detail,

subtlety and possibility for manipulation that would have been not only impossible but ludicrous as part of the original proposal.

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FIGURE LEGENDS

Figure 1: Illustrated schematically are cortical neurons receiving input from the two eyes. During monocular deprivation, open eye input activity continues to drive the cortical neuron. Under these conditions, the synaptic response to closed eye input is weakened. In contrast, no rapid modifications occur during binocular deprivation when the cortical neuron is not active. These considerations led Stent (1973) to propose that postsynaptic activity is a necessary condition for synaptic modification, and that the sign of the modification depends on the concurrent level of input activity.

Figure 2: Extension of the Stent model, introduced by Wolf Singer (1979), to incorporate the neuromodulators, acetylcholine (ACh) and norepinephrine (NE), which appear to be necessary for synaptic modification during monocular deprivation.

Figure 3: In order to test the hypothesis that postsynaptic activation is a necessary condition for synapse modification in the striate cortex, Reiter and Stryker (1988) monocularly deprived kittens as area 17 was infused with the GABA agonist muscimol. When the activity blockade wore off, they assayed the ocrtex for changes in ocular dominance (OD). Shown here are the ocular dominace histograms (replotted using a 5 point OD scale); bar height indicates the percentage of neurons in each OD

category. Filled and open circles indicate the OD categories containing neurons responsive only to deprived eye or open eye stimulation, respectively.

Figure 4: The BCM modification function.

Figure 5: A period of binocular deprivation (BD) decreases the value of the modification threshold, and therefore changes the shape of ϕ.

Figure 6: Cartoon to illustrate the 2 types of excitatory amino acid (EAA) receptor and the ionic conductances they activate. Note that the NMDA (N) receptor activates a calcium conductance, but only when the Mg++ block is lifted at depolarized membrane potentials. Q is meant to represent the quisqualate subtype of EAA receptor.

Figure 7: Data from the work of Kleinschmidt, Bear and Singer (1987) showing the effects of NMDA receptor blockade on the response of visual cortex to monocular deprivation. Increasing extracellular concentrations of APV (estimated concentrations are indicated) increases the percentage of neurons with binocular, unoriented receptive fields.

Figure 8: Data from the work of Bear, Gu, Kleinschmidt and Singer (submitted for publication) showing the effects of high [APV] on the cortical response to monocular deprivation. The responses of most

neurons near the infusion cannula are dominated by the deprived eye. Conventions for the OD histograms are as for figure3.

Figure 9: Cartoon to show the recently characterized EAA receptor site (I) that is linked to PIns turnover. The receptor is linked via a G protein to the enzyme phospholipase C (PLC) which hydrolyzes phosphatidyl inositol-4,5 biphosphate (PIP_2) to produce inositol triphosphate (IP_3) and diacyl glycerol (DG). Both IP_3 and DG function as intracellular second messengers.

Figure 10: TOP: Visual cortical plasticity as a function of age, estimated by Blakemore and van Sluyters (1974) using reverse suture and Olson and Freeman (1980) using monocular deprivation. BOTTOM: Postnatal changes in ibotenate stimulated PIns turnover in kitten striate cortex (from Dudek and Bear, submitted for publication).

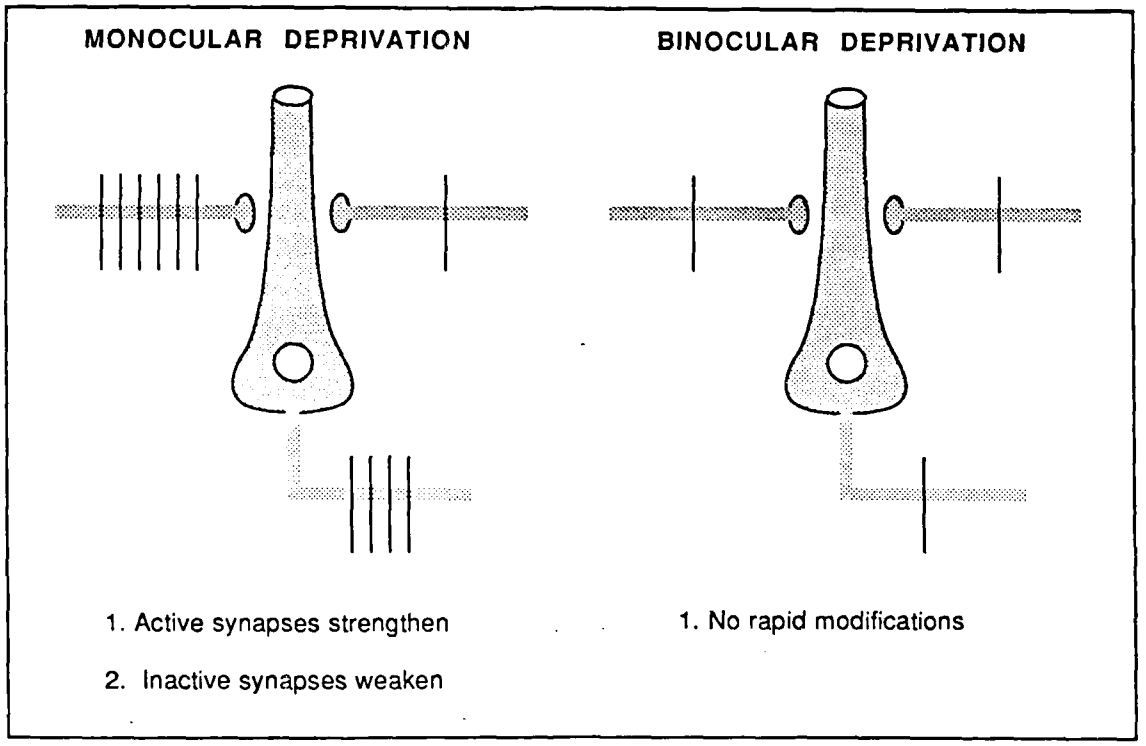
Figure 11: Data from the work of Neve and Bear (1988) showing expression of growth associated protein GAP43, calcium calmodulin dependent protein kinase II (CaM kinase II), glutamic acid decarboxylase (GAD) and Alzheimer amyloid precursor protein (APP) genes in striate cortex of dark-reared and age-matched normal kittens (P40-50). In order to reduce the variance, all individual values in (A) are normalized against those for the MAP2 gene, which did not change significantly under the conditions tested (B).

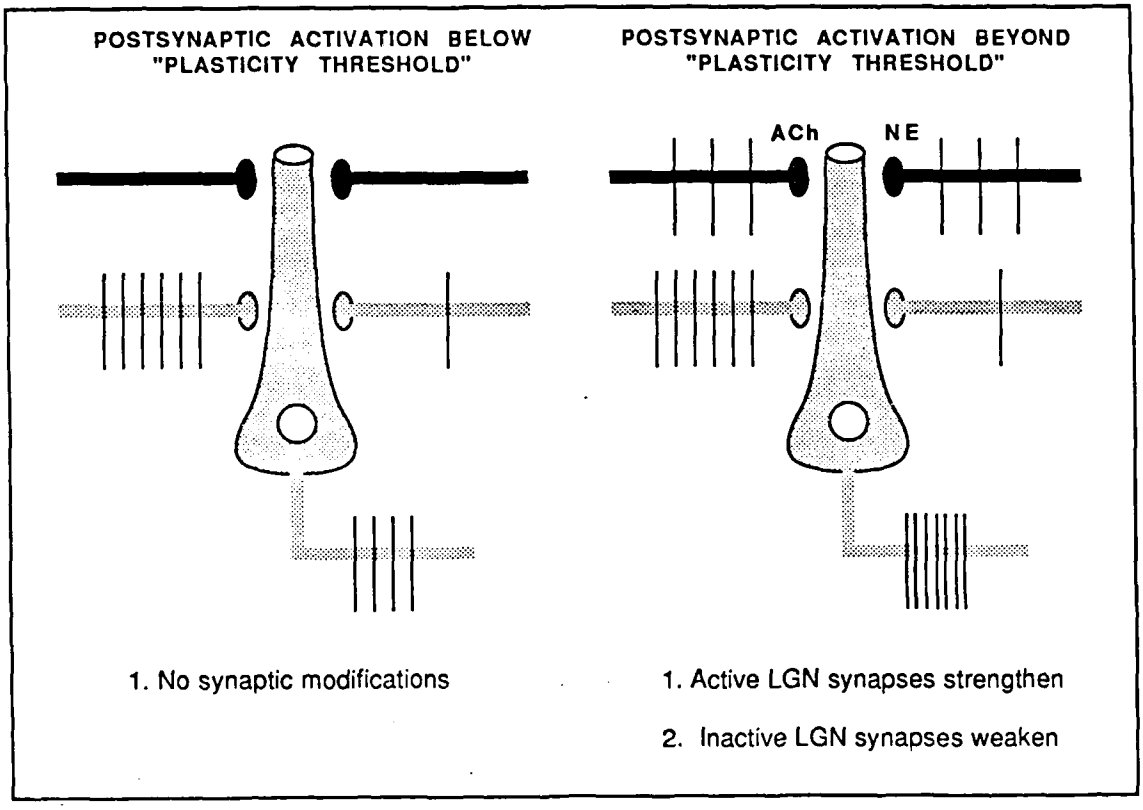
Figure 12: Data from the work of Sherin, Feldman and Bear (1988) showing NMDA stimulated ^{45}Ca uptake by slices of striate cortex from normally reared 4-6 week old kittens and age-matched kittens that had been binocularly deprived for 4 days prior to sacrifice. In A uptake is expressed in nmoles per mg protein; in B uptake is expressed as the percentage of maximum uptake.

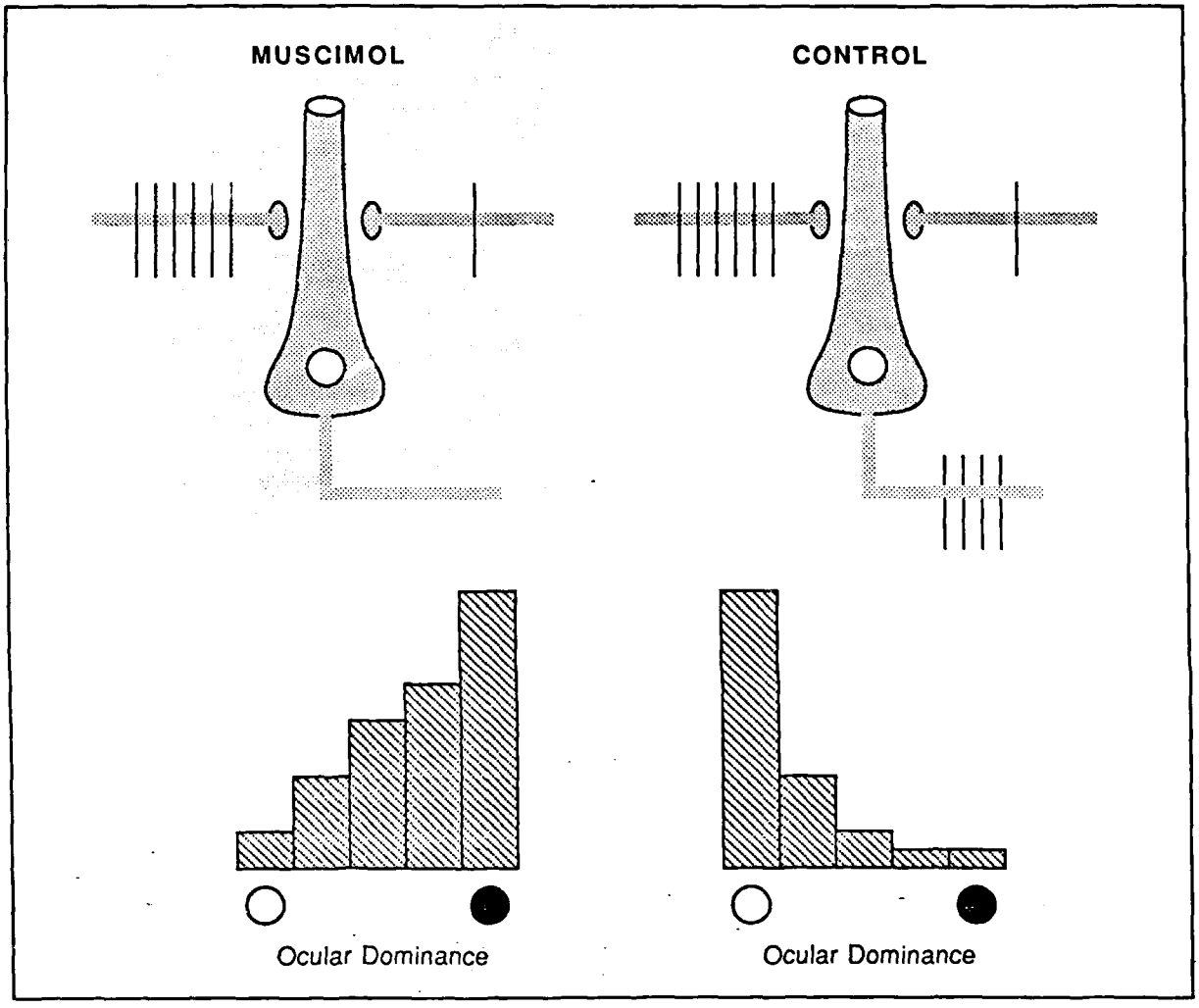
Figure 13: A molecular model for synapse modification in the striate cortex. According to this model, changes in the efficacy of an active synapse depend on the balance between postsynaptic signals linked to activation of NMDA ("N") and non-NMDA ("Q") receptors. See text for further explanation.

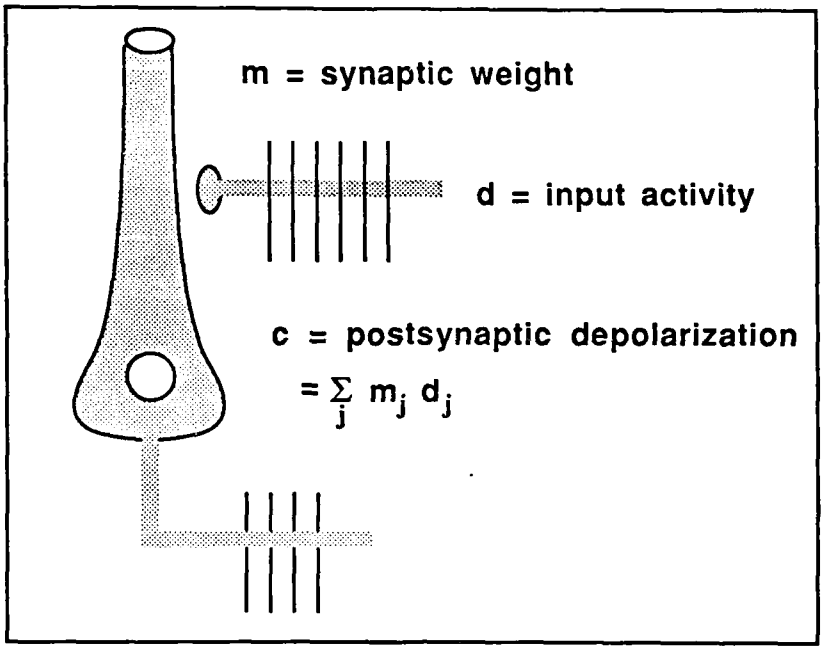
Figure 14: A neural network in which every neuron receives inputs from the LGN and from each other. In B, using a mean field approximation, all other cortical neurons are replaced by an "effective cell", and the individual effects of the intracortical connections are replaced by their average effect (α), assumed to be inhibitory.

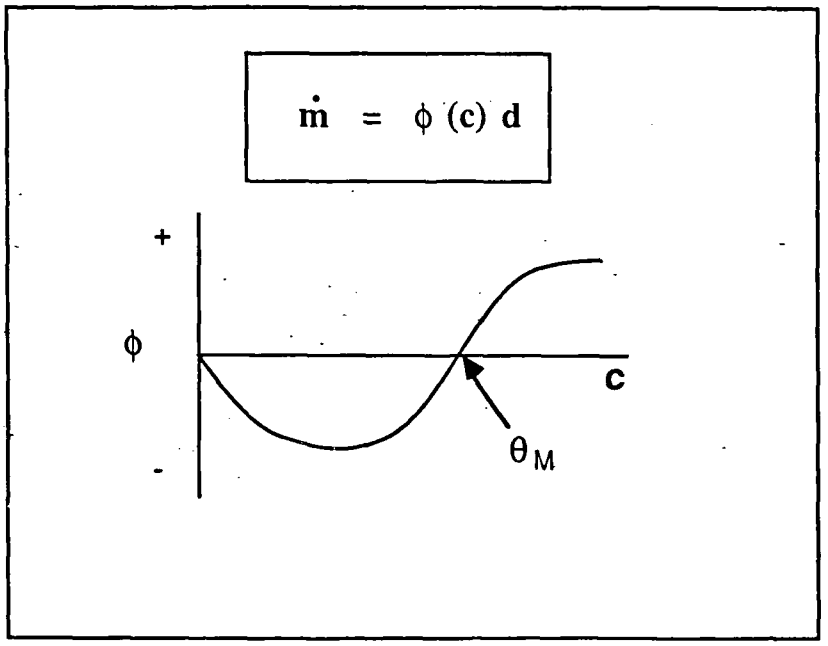
Figure 15: Incorporation of inhibition into the model of figure 13. When input activity is coincident with strong inhibition (B), the balance of postsynaptic second messenger signals favors the non-NMDA receptors, and the active geniculocortical synapses weaken.


MONOCULAR DEPRIVATION
BINOCULAR DEPRIVATION
1. Active synapses strengthen
2. Inactive synapses weaken
1. No rapid modifications

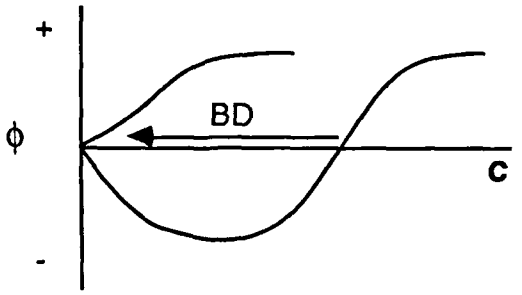

POSTSYNAPTIC ACTIVATION BELOW "PLASTICITY THRESHOLD"
POSTSYNAPTIC ACTIVATION BEYOND "PLASTICITY THRESHOLD"
ACh
NE
1. No synaptic modifications
1. Active LGN synapses strengthen
2. Inactive LGN synapses weaken


MUSCIMOL
CONTROL
Ocular Dominance
Ocular Dominance


m = synaptic weight
d = input activity
c = postsynaptic depolarization
$= \sum_j m_j d_j$

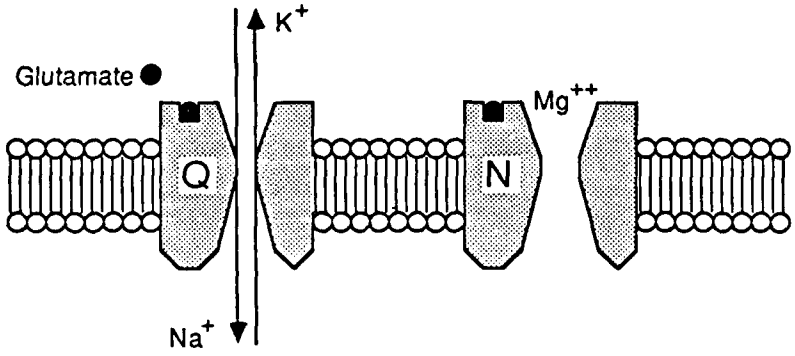

$\dot{m} = \phi(c)\, d$
+
ϕ
-
c
θ_M

Bear & Cooper fig 5

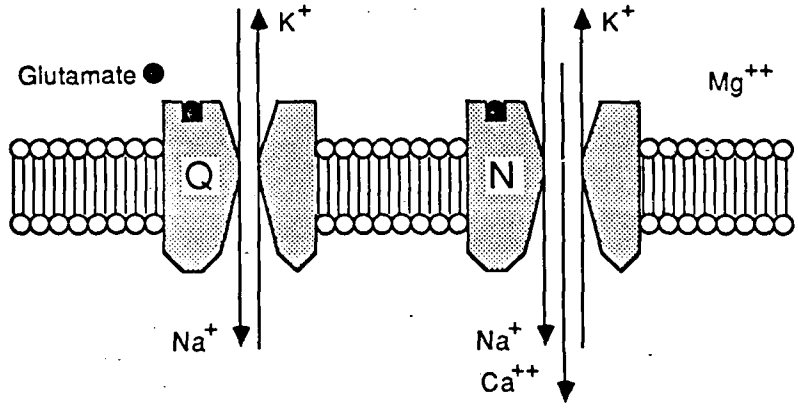


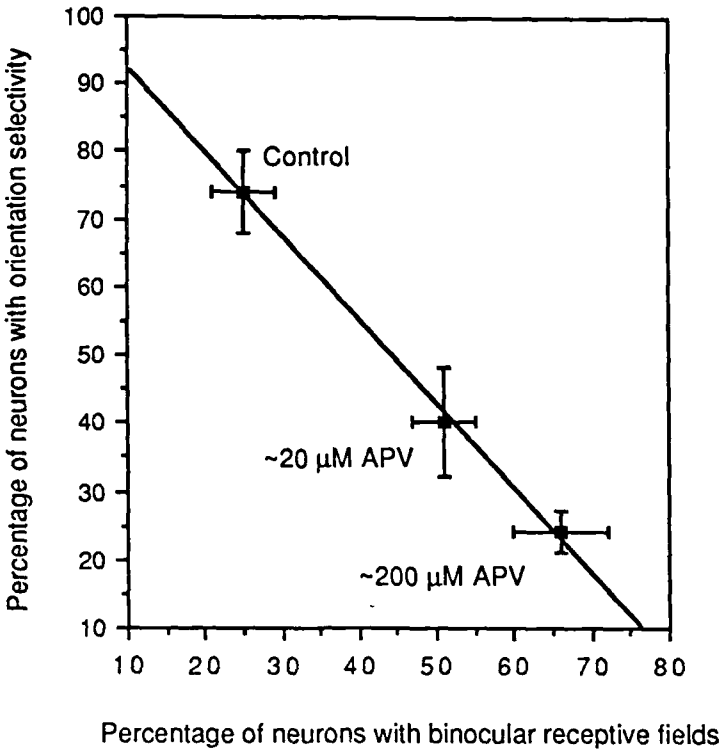
POSTSYNAPTIC RESPONSE TO GLUTAMATE

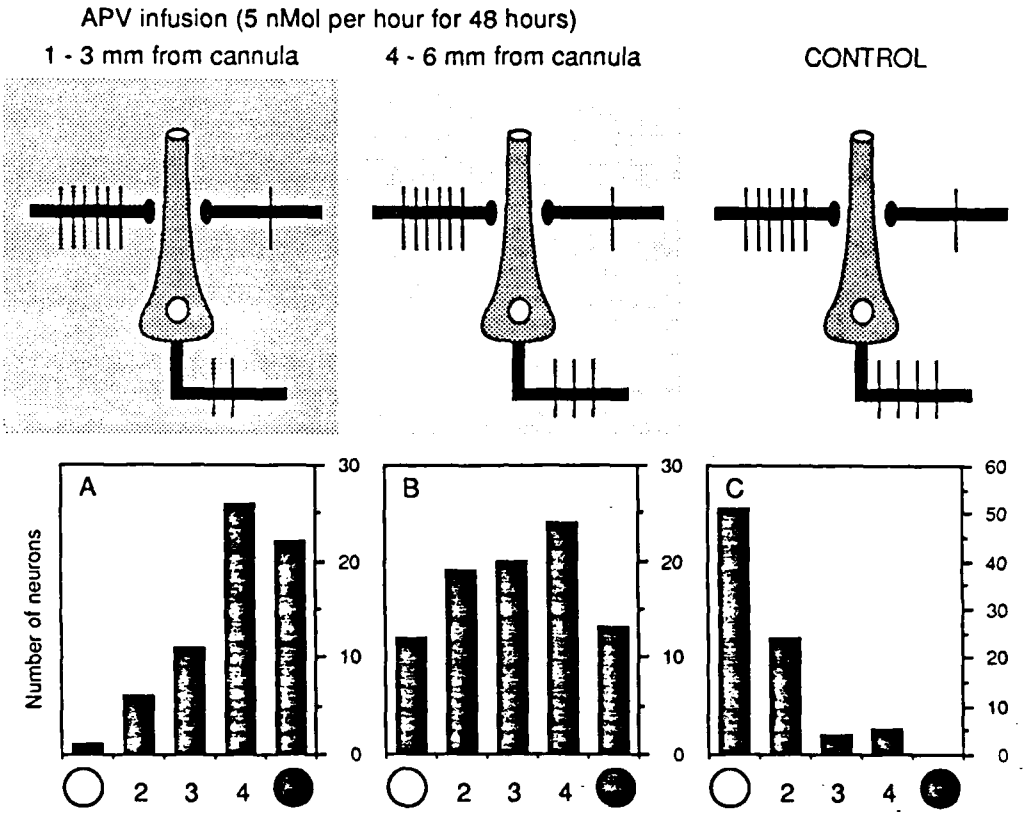
(1) AT RESTING MEMBRANE POTENTIAL

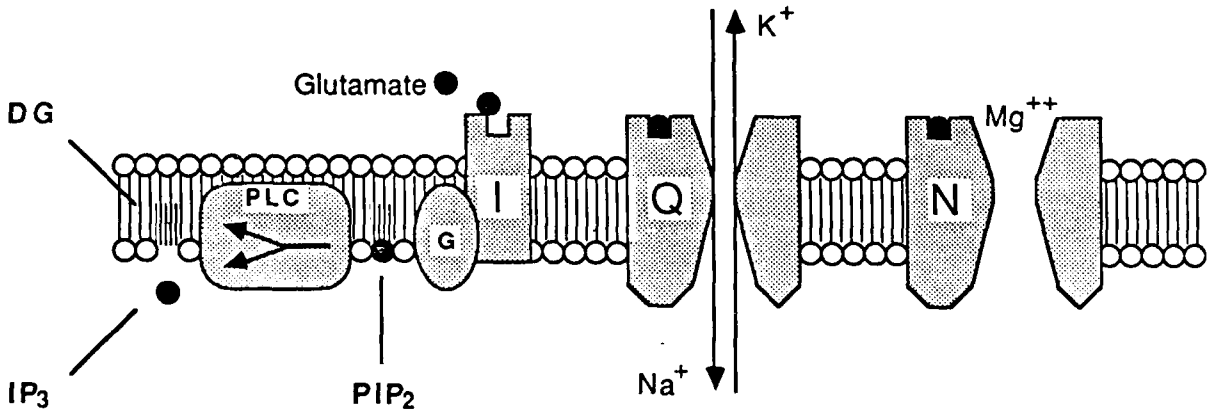


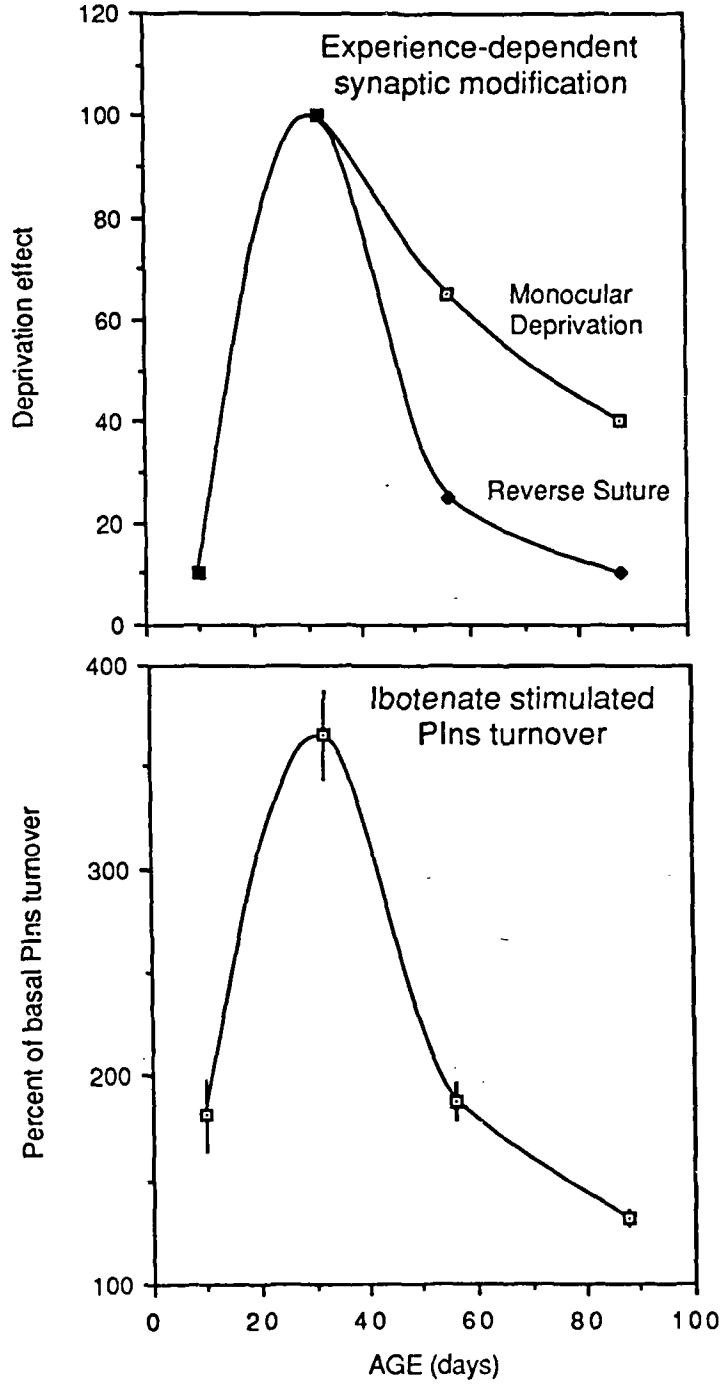
(2) AT DEPOLARIZED MEMBRANE POTENTIALS



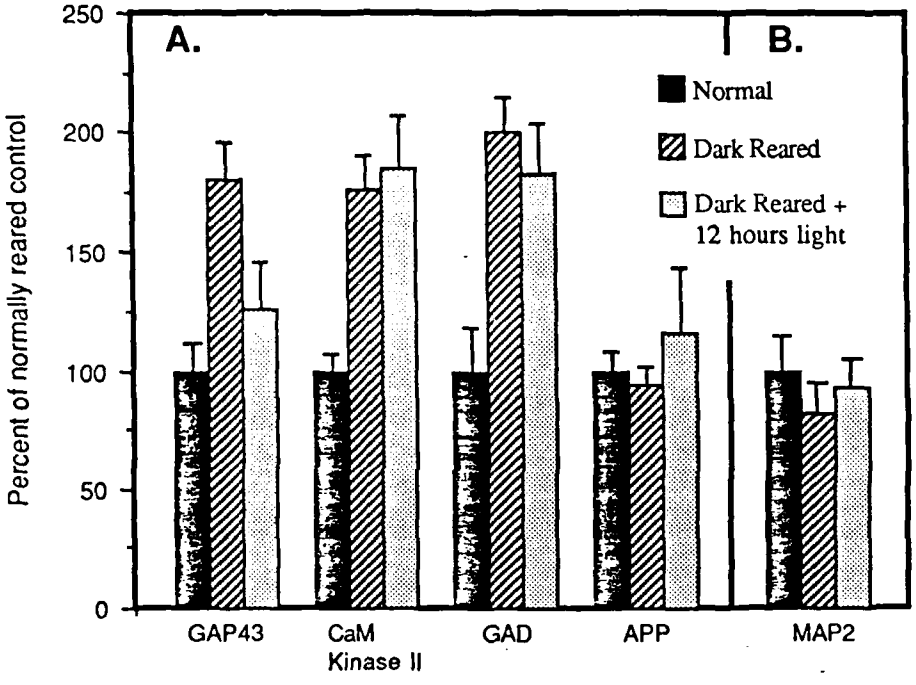

Percentage of neurons with orientation selectivity
100
90
80
70
60
50
40
30
20
10
Control
~20 µM APV
~200 µM APV
10
20
30
40
50
60
70
80
Percentage of neurons with binocular receptive fields

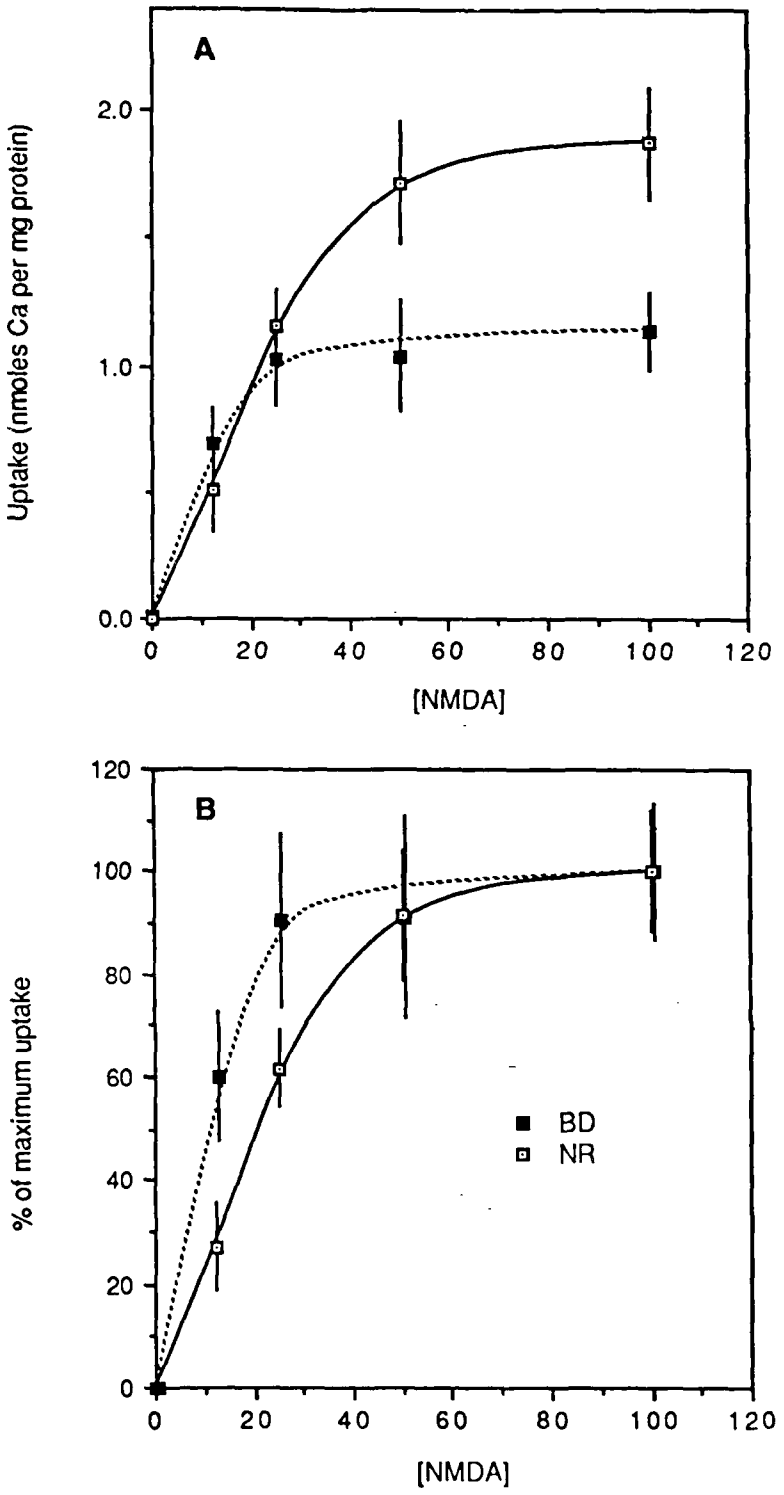

APV infusion (5 nMol per hour for 48 hours)
1 - 3 mm from cannula
4 - 6 mm from cannula
CONTROL
A
B
C
Number of neurons
30
20
10
0
60
50
40
30
20
10
0
2
3
4

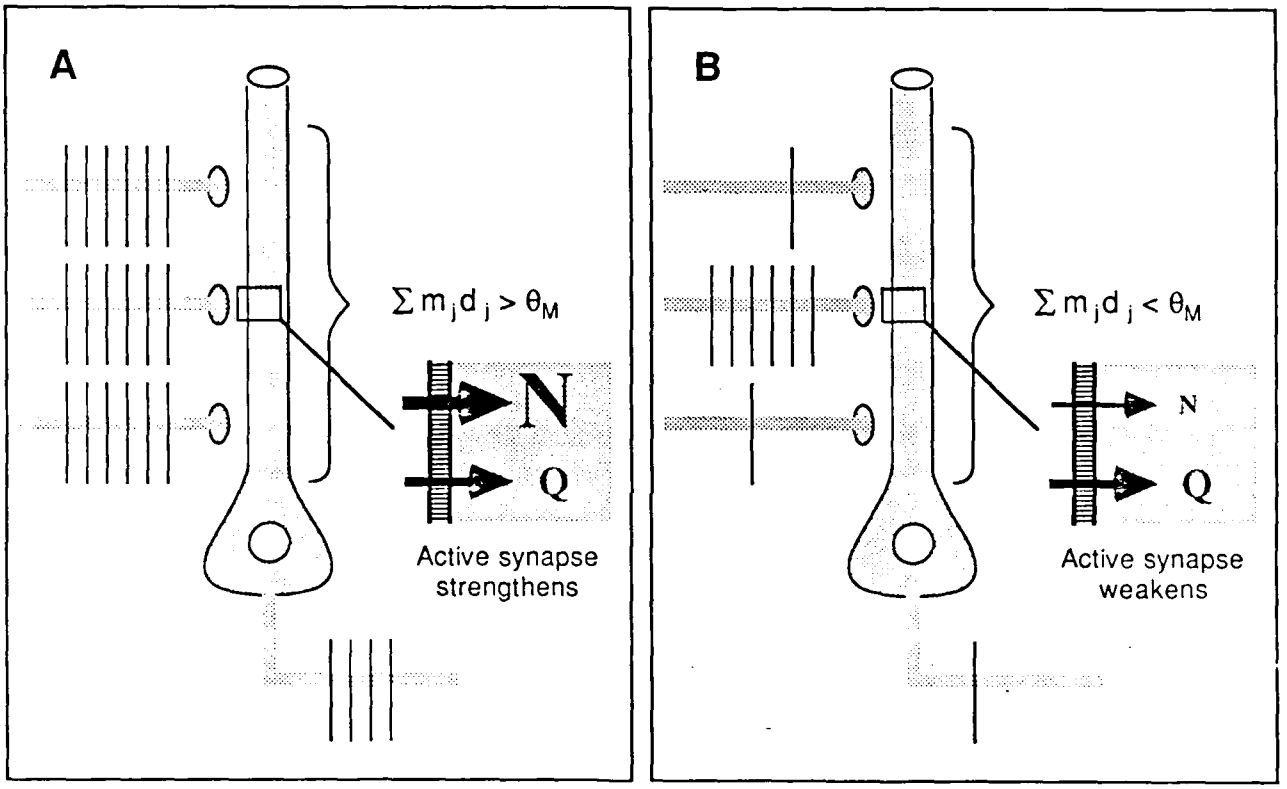

K+
Glutamate
DG
Mg++
PLC
G
I
Q
N
IP3
PIP2
Na+

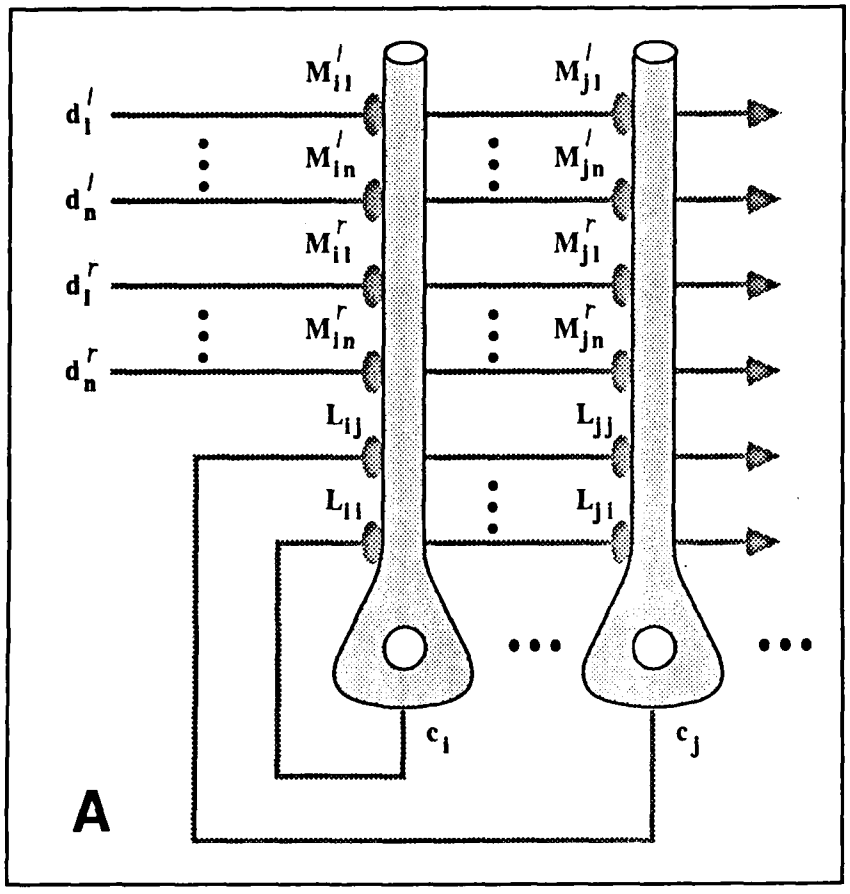

Experience-dependent
synaptic modification
Deprivation effect
120
100
80
60
40
20
0
Monocular
Deprivation
Reverse Suture
Ibotenate stimulated
PIns turnover
Percent of basal PIns turnover
400
300
200
100
0
20
40
60
80
100
AGE (days)

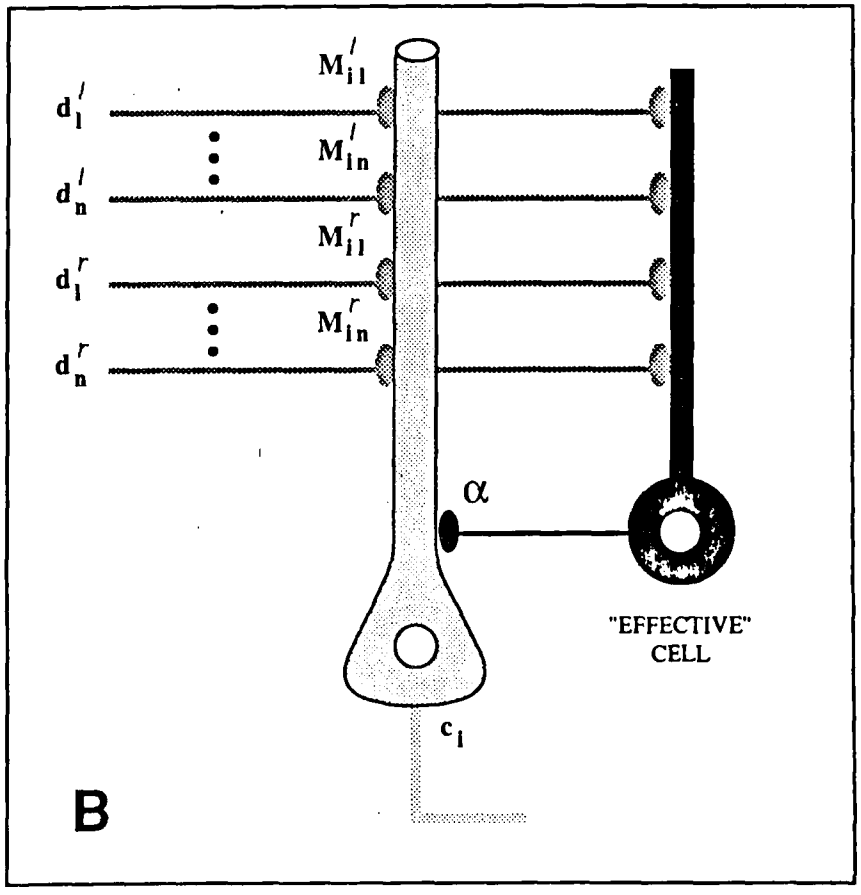
Bear & Cooper fig 11

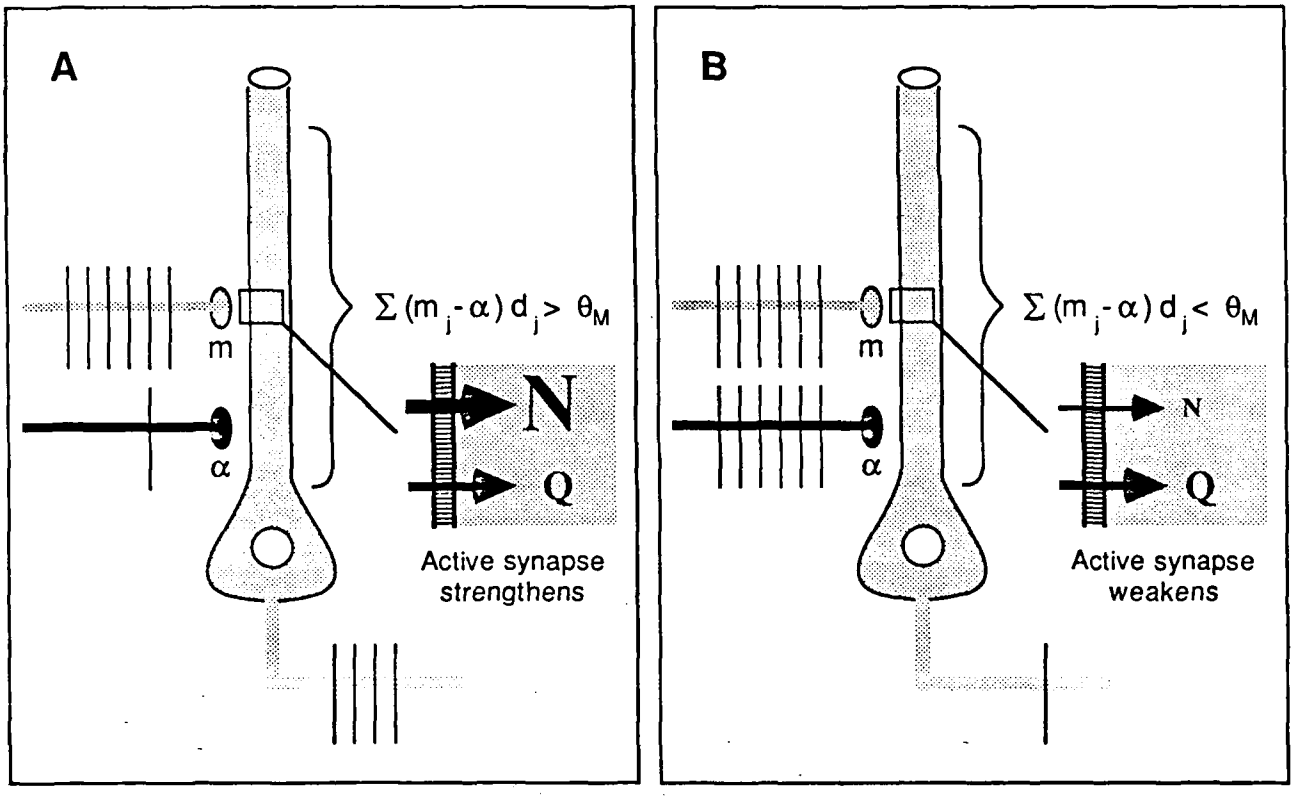



A
2.0
1.0
0.0
Uptake (nmoles Ca per mg protein)
0
20
40
60
80
100
120
[NMDA]
B
120
100
80
60
40
20
0
% of maximum uptake
BD
NR
0
20
40
60
80
100
120
[NMDA]


A
$\Sigma m_j d_j > \theta_M$
N
Q
Active synapse strengthens
B
$\Sigma m_j d_j < \theta_M$
N
Q
Active synapse weakens


d_1^l
d_n^l
d_1^r
d_n^r
M_{i1}^l
M_{in}^l
M_{i1}^r
M_{in}^r
M_{j1}^l
M_{jn}^l
M_{j1}^r
M_{jn}^r
L_{ij}
L_{ii}
L_{jj}
L_{ji}
c_i
c_j
A


d_1^l
d_n^l
d_1^r
d_n^r
M_{i1}^l
M_{in}^l
M_{i1}^r
M_{in}^r
α
"EFFECTIVE" CELL
c_i
B


A
m
α
Σ (m_j - α) d_j > θ_M
N
Q
Active synapse
strengthens
B
m
α
Σ (m_j - α) d_j < θ_M
N
Q
Active synapse
weakens